Annual Historical Report, CY 2005

U.S. Army Medical Materiel Development Activity (USAMMDA)

Calendar Year (CY) 2005

Submitted by:
USAMMDA
1430 Veterans Drive
Fort Detrick, MD 21702
http://www.usammda.army.mil

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U.S. ARMY MEDICAL MATERIEL DEVELOPMENT ACTIVITY (USAMMDA)

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OUR MISSION

We will develop and manage medical materiel to protect and sustain the Warfighter on point for the Nation.

OUR VISION

We will integrate with U.S. Army Medical Research and Materiel Command (USAMRMC), Federal agencies, and the Department of Defense (DoD), as part of the joint biomedical research and materiel community, to focus on delivering the best medical solutions for today and tomorrow.

Our products will be an integral part of the DoD Force Health Protection Program, to include vaccines, drugs, and medical devices, to prevent, diagnose, and treat infectious diseases, combat-related casualties, and Chemical, Biological, Radiological, Nuclear & Explosive (CBRNE) threats.

Our products will enhance far-forward medical care across the full spectrum of health care missions worldwide.

OUR PERSONNEL

Based on a directive from the Commander of the U.S. Army Medical Research and Materiel Command (USAMRMC) to realign several agencies within the MRMC, (Memorandum dated 29 September 2004), this year officially began the integration of one of those agencies into USAMMDA. Approximately 18 staff members of the Regulatory Affairs Division, formerly under the purview of the U.S. Army Research Institute of Infectious Diseases (USAMRIID), were added to USAMMDA by implementation of that memo. We gained several new hires and lost some of our civilian employees due to retirement. Some of our Military personnel were promoted during this year.

Matrix support continues to be provided to other organizations through a Memorandum of Agreement between USAMRMC and the parent organizations. This includes six civilians to the Chemical, Biological Medical Systems (CBMS); one civilian and two officers to the MC-4, Enterprise Information Systems; two officers to the Telemedicine and Advanced Technology Research Center (TATRC), and one officer and three civilians to the USAMRMC.

The following table presents a comparison between 2004 and 2005 personnel strength. Overall, USAMMDA strength continues to vary between 80 and 90.

2004 PERSONNEL PROFILE

Required	Authorized	Actual
74	38	64

2005 PERSONNEL PROFILE

Required	Authorized	Actual
80	42	90

FISCAL 2005 PERFORMANCE

In-House: In FY05, USAMMDA's In-House fiscal execution of direct core funds fell short of the USAMRMC obligation and disbursement targets by 21 percent and 2 percent respectively. This is largely attributed to Congressional funds ($3.1M) received in PA 836 for an unknown product for which guidance was not received until after calendar year-end. The FY05 In-House total direct funds included tech base funds ($70K) for quality assurance monitoring, Congressional funds ($43.6M), and DHP funds ($2.5M) for HIV, Adenovirus, Anthrax, Flu Vaccine, RCQ and Force Health Protection-Investigational New Drug* (FHP-IND) support.

	In-House (Core-Direct)		
	Allotment	**Obligations**	**Disbursements**
Fiscal 2005 Dollars ($000)	17,013	12,505	9,108
Target (%)		95	56
Actual (%)		74	54

In addition, USAMMDA In-House managed $4.3M in reimbursable funds in FY05. This included funds from the Chemical Biological Medical Systems (CBMS) and PM-Medical Communications for Combat Casualty Care (PM-MC4) offices for matrix support personnel. In addition, reimbursable funds were received from the Marine Corps, Defense Threat Reduction Agency (DTRA), Air Force Medical Evaluation Support Activity (AFMESA) and from U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), U.S. Army Medical Materiel Activity (USAMMA), and Walter Reed Army Institute of Research (WRAIR) for various task order services.

Program Wide: The laboratory program's FY05 obligations exceeded the target by 2 percent and the disbursement target was exceeded by 27 percent. Obligations

and disbursements for extramural funds fell below established targets by 41 and 39 percent, respectively. In FY05, extramural funds consisted of tax dollars. Performance in the total Command-wide development program fell below the obligation target by 10 percent, and 11 percent below the disbursement target. In addition, FY05 total program direct funds reflect a $1.2M increase from FY04 funding. Fiscal execution performance at the project level is provided on the next page.

Program-Wide (Core-Direct)

	Allotment	Obligations	Disbursements
Fiscal 2005 Dollars ($000)	25,508	20,890	15,273
Target (%)		95	56
Actual (%)		82	60

In FY05, USAMMDA managed a total of $43.6M of Congressional funds. FY05 Congressional funds were received for Plasma Sterilizer, Life Support for Trauma and Transport (LSTAT), Chitosan Hemorrhage Control Dressings and Bandage Component, Emergency I.V. System, Cartledge Infuser, Compact Lightweight Full-Feature Patient Monitor w/Defibrillator, Leishmaniasis Preventive Treatment Diagnosis, Light-Based Self Treatment for Pseudofolliculitis, Future Medical Shelter System, Portable Oxygen Generator, Electro-osmotic Pain Therapy System for Adjustable Rate Implant Drug Delivery, and Hemoglobin Based Oxygen Carrier (HBOC). In total, including direct, reimbursable, and Congressional funding, USAMMDA managed $75M of funds in FY05.

FISCAL 2005 PROGRAM EXECUTION

DIRECT – ADVANCED DEVELOPMENT									
		PERCENT							
	Allotment	In-House		Lab		Extramural		Total	
Project	($000)	OBL	DISB	OBL	DISB	OBL	DISB	OBL	DISB
808	5251	92	63	100	89	100	4	97	73
836	7322	41	34	100	100	100	5	46	32
837	712	96	75	97	97	100	58	97	82
Total 6.4	**13,285**	**54**	**42**	**99**	**89**	**100**	**8**	**69**	**51**
812	3565	97	65	100	89	100	43	99	81
832	4258	97	94	0	0	100	58	97	91
834	1010	99	77	83	83	100	1	92	78
849	3390	91	28	99	75	100	0	92	28
Total 6.5	**12,223**	**95**	**67**	**97**	**87**	**100**	**34**	**96**	**70**
Total Adv Dev	**25,508**	**74**	**54**	**98**	**88**	**100**	**21**	**82**	**60**
Tech Base	70	100	28	0	0	0	0	100	28
DHP	2533	100	48	0	0	0	0	100	48
Congressional	42561	94	36	92	67	28	15	88	35
Total Direct	**70,672**	**89**	**42**	**97**	**83**	**54**	**17**	**87**	**45**

REIMBURSABLE									
		PERCENT							
	Allotment	In-House		Lab		Extramural		Total	
Project	($000)	OBL	DISB	OBL	DISB	OBL	DISB	OBL	DISB
CBMS	1,939	98	54	0	0	0	0	98	54
Other Reimb	2,382	31	24	0	0	0	0	31	24
Total Reimb.	**4,321**	**61**	**37**	**0**	**0**	**0**	**0**	**61**	**37**

TOTAL PROGRAM MANAGED									
		PERCENT							
	Allotment	In-House		Lab		Extramural		Total	
Project	($000)	OBL	DISB	OBL	DISB	OBL	DISB	OBL	DISB
Total Program	**74,993**	**87**	**42**	**97**	**83**	**54**	**17**	**85**	**45**

APPLIED MEDICAL SYSTEMS PROJECT MANAGEMENT DIVISION

Introduction

The Applied Medical Systems Project Management Division (AMSPMD) is a multidisciplinary team with broad mission capabilities for the advanced development of medical products used to sustain and support the Warfighters. The team consists of both product managers and model makers, who have expertise in project management, engineering, fabrication, and technical testing. The product managers analyze functional requirements, conduct market investigations, and develop and execute technical and program strategies and plans for all acquisition program phases from pre-Milestone A through Full-Rate Production.

The product managers also direct program resources, and defend program content and structure during science and acquisition forums. The focus for the Division is an early involvement with products that are within the technology base, resulting in streamlined development efforts by combining Milestones and transitioning medical products rapidly to the logistician for procurement and fielding. As a result of this emphasis, product managers are busy with many products either developing and executing broad acquisition strategies or monitoring technology base research efforts. Examples of active products include: Ceramic Oxygen Generator; Dental Field Treatment and Operating System; Future Medical Shelter System; Future Combat Systems — Medical Variants; Hemostatic Dressing; Rotary Valve Pressure Swing Adsorption Oxygen Generator; Ventilatory Assist Device; Plasma Sterilizer; and Battery-Powered IV Fluid Warmer.

Military Relevance

The AMSPMD designs, develops, and tests field medical equipment in support of battlefield combat casualties. The AMSPMD specializes in developing new and innovative breakthrough technology as well as adapting and hardening commercial-off-the-shelf (COTS) systems for joint military applications. For example, AMSPMD personnel were intimately involved with the development of the Special Medical Emergency Evacuation Device (SMEED). More than 700 SMEED systems were deployed with Army, Marine, and Air Force units in support of Operations Enduring (OE) and Iraqi Freedom (OIF).

Cartledge Infuser

The Cartledge Infuser (CI) is intended to allow a physician to normalize a patient’s hemodynamic status. The CI is a variable rate infusion pump that allows a physician to replace blood volume at flow rates ranging from 20 ml per hour through 1200 ml per minute. A blood warming system is incorporated into the design and provides optimal blood warming at any flow rate. The CI operates on

standard alternating electrical power, and is capable of battery operation for up to one hour. It weighs approximately 18 pounds, and is 14 inches wide, 8 inches high and 8 inches deep.

The manufacturer, Smisson-Cartledge Biomedical, completed most of the manufacturing during CY05. The company submitted its 510(k) application for the CI to the U.S Food and Drug Administration (FDA) in July 2005.

Ceramic Oxygen Generator

The Ceramic Oxygen Generator (COG) project is developing leading edge technology for the production of high purity, medical grade oxygen. This type of oxygen generator has an advantage over conventional methods such as pressure swing adsorption by generating very high purity oxygen without using any moving parts. This system uses a metal/ceramic membrane matrix to avoid the cracking and sealing problems that have been experienced by other developers attempting to commercialize COGs.

The oxygen generator prototype has been assembled and is being tested by the contractor. Improvements to the cell design have doubled the oxygen output without affecting durability or efficiency. A lightweight lithium-polymer battery and charger have been designed and built as have the electronic controls; these components are being integrated into a complete oxygen generator. This Activity also assisted by machining precision welding fixtures for the manufacture of the oxygen generator cells.

Chitosan Bandage Component

Production of the Hemorrhage Control (Chitosan) Dressing (see below) is dependent on materials imported from Iceland. This is because U.S. suppliers are currently unable to provide medical grade chitosan in sufficient quantity and purity. The objective of the Chitosan Bandage Component program is to establish a U.S.-based chitosan production facility to support production of hemorrhage control dressings for military and civilian use.

This work is in its early stages, and is currently focused on assessment of biological and manufacturing variables that affect the quality of chitin (chitosan precursor) obtained from purpose-bred shrimp, development of regulatory compliant procedures for large-scale production of medical grade chitosan, and development and analysis of chemical derivatives of chitosan that could potentially offer greater hemostatic and anti-bacterial efficacy.

Coliform Analyzer

The Coliform Analyzer was transisitioned to this organization for advanced development in FY05. The developer of the Coliform Analyzer is Pacific Technologies in Redmond, Washington. This device uses the fluorescence of nutrients that are selectively used by E. Coli bacteria. After a short incubation time, the collected water sample is illuminated by a set of light emitting diodes (LEDs) and any fluorescence is observed. This analyzer is able to detect contamination in water that will have to be rejected in less than an hour; in eight hours it verifies that water is OK for use. It takes less time to detect contaminated water than it does to certify that water is good because proving that water is good requires enough time for the bacteria to multiply to detectable levels.

Pre-production devices will be fabricated in FY 06 for EPA Test Method Certification.

Critical Care System for Trauma and Transport

The requirement for a Critical Care System for Trauma and Transport (CSTAT) describes a single-patient, intensive care capability that will be used to maintain life support and stabilization of battlefield casualties during evacuation. The CSTAT requires incorporation of a defibrillator, ventilator, vital signs monitor, infusion pumps for fluid resuscitation and administration of medications, suction unit, and self-contained oxygen supply in a unit that attaches to a standard North Atlantic Treaty Organization (NATO) litter.

The Life Support for Trauma and Transport (LSTAT), which was cleared for marketing by the FDA, satisfies the majority of the CSTAT requirements. The contractor is currently modifying the LSTAT to fully satisfy those requirements, especially the weight requirement. The next generation LSTAT will feature a new modular design and will weigh roughly half as much as the current system. The Defense Advanced Research Projects Agency also provided funding to develop an even lighter version called the LSTAT-Lite, which will have somewhat less functionality than either the current or next generation LSTAT, but will only weigh about a fourth as much as the current system.

The current LSTAT system was given a fleet-wide airworthiness release by the U.S. Army Aviation and Missile Command for use on all UH-60 helicopters, and it was given Air Force clearance for use on KC-l35 fixed-wing aircraft.

The White House Medical Unit continued to employ LSTAT systems in its operations. A small number of LSTAT systems were also deployed with Army and Navy units in support of OEF/OIF. During its wartime deployment, the LSTAT was

used as a medical evacuation platform, intra-hospital transport platform, intensive care bed, and surgical platform.

Dental Field Treatment and Operating System

The Dental Field Treatment and Operating System (DEFTOS) incorporate the latest technology to provide a modern, lightweight dental system for field operations. It reduces the need for compressed air and thus large power generator capacity in the field. The unit incorporates an electric hand piece, which produces superior torque compared to previous systems.

During CYO5, 130 DEFTOS units were procured for fielding. Thirty of the first units were deployed to Iraq for long-term first article evaluation. Some problems were encountered because of the "dirty" commercial power available. During the first two months of use, the systems were used to perform over 3 million dollars worth of dental work. The systems are being used in a sustaining mode, and support American and coalition troops as well as the indigenous population.

Emergency IV System

The Emergency IV System is designed to eliminate the dependence on gravity and the traditional IV pole. Using a pressurized bag within a bag technology, an IV system can be developed, which is independent of gravity, uses no batteries, and has no motors.

This is a Congressional Special Interest product, and the funds were not available until late in the fiscal year. The manufacturer, Northwind Technologies, Anchorage, AK, has obtained facilities and is equipping them. An integrated product team (IPT) meeting was convened with the manufacturer, the Combat Developer, and the Materiel Developer to identify the military need. Product design has been initiated, and prototype fabrication will begin in late FY06.

Fibrinogen Bandages for Battlefield Wounds

The Fibrinogen Bandage (FB) is intended to provide a revolutionary improvement in the control of severe life-threatening hemorrhage. The FB will be composed primarily of human fibrinogen and other blood clotting proteins obtained from transgenic livestock, human plasma, or a combination thereof. Once commercialized, the FB will be used by the combat medic/combat lifesaver and other medical personnel on the battlefield.

The current focus of this program is to develop an economical and abundant source of fibrinogen and associated FDA-compliant purification methods to be used for a fibrin dressing. So far, the University of Nebraska-Lincoln, who is doing this work, has had success in attaining recombinant human fibrinogen from transgenic cows. The University of Nebraska is working with an industrial partner, STB Ltd., towards development of a prototype dressing.

Field Sterilizer Improvement Device

The field sterilizer currently in use is a well-proven piece of equipment. One of the shortcomings has been its high water consumption; it uses 2.5 gallons of water every time it sterilizes a load of materials. A water recovery device was developed before Operation Desert Storm (ODS). To meet the immediate need, the prototype was put into production before completely optimizing the design. The manufacturer of the ODS-designed water recovery system designed an improved version. The new version will need testing to verify its performance and ruggedness.

The FSID was added to the Unit Assemblage for the Central Medical Supply to equip existing hospitals.

Future Combat Systems — Medical Variants

The Future Combat System (FCS) — Medical Vehicle-Evacuation (MV-E) and Medical Vehicle-Treatment (MV-T) will function as the ground medical evacuation and treatment assets in the Unit of Action. Medical capability will include an automated litter lift system, on-board oxygen generation, suction, storage space for essential medical items and equipment, automated data management, plus the capacity to carry four litter patients or six ambulatory patients and a crew of three (MV-E), or provide interior space for the treatment of two patients and a crew of four (MV-T).

Systems unique to the MV-E such as the blood refrigerator and oxygen system are now technically ready, but the vehicle manufacturer and integrator have to supply their requirements to make the final engineering decisions.

The FCS Operational Requirements Document (ORD) requirements were reviewed and approved by the Joint Requirements Oversight Council as of January 31, 2005. There are 25 Medical Variant specific requirements. The program is 2.5 years into the System Development and Demonstration Phase.

BAE Systems, the FCS-MV Vehicle Integrator, produced a mock-up of the MV-E

at the Santa Clara, CA, facility. A bread-board litter-lift system was also fabricated. The litter system was reviewed by the MV IPT and many changes occurred to make the system more functional to the requirements. An MV-T prototype tent was fabricated at Natick, and alternative tents are being investigated.

Future Medical Shelter System

The Future Medical Shelter System (FMSS) is a multifaceted program which leverages Congressional funding to explore advanced rigid and soft-walled shelters for forward deployed healthcare providers. The objectives of the FMSS program are: (1) to develop a self-contained emergency response package for use by Forward Surgical Teams (FST); and (2) to develop a replacement for the Deployable Medical System (DEPMEDS) operating room shelter, which has reduced weight and enhanced transportability and deployability. These efforts consist of chemically/biologically-hardened International Standards Organization (ISO) shelter with quick erect/strike times and integrated electrical, water, and medical packages, and provide 1200 square feet of soft tentage as patient care wards. Three development efforts are underway:

Mobile Medical International Corporation (MMIC) prototype was developed and user-tested at Camp Bullis by the U.S. Army Medical Department Board (AMEDDBD) in May 2005. The MMIC is working on second generation prototypes for a second round of user testing, and first round mil-spec testing and ColPro testing to occur in September 2006 at Camp Bullis.

EADS developed a 3:1 expandable ISO shelter configured as an operating room. The support ward module using “Air-Cell” technology for the tentage is underway. First-round user testing will occur in September 2006 at Camp Bullis.

The Oakridge National Laboratories prototype was developed and user-tested by the AMEDDBD at Camp Bullis in May 2005.

Haemonetics ACP 215

The Haemonetics ACP 215 is an automated, closed-loop blood processor designed to make thawed blood ready and safe for transfusion use. It extends the shelf life of thawed blood from 24 hours to 14 days.

The objective of this program was to expand the indicated use of the ACP 215. This system is currently being used by the Armed Services Blood Program Office. The manufacturer conducted three clinical studies to support new indications,

which were essential to the use of the ACP 215 for contingency and daily use within the Department of Defense. The three clinical trials examined the effects of different frozen blood storage temperatures, blood freezing methods, additive solutions, and blood storage bag types on thawed blood quality and subsequent patient safety. The studies were successful and the FDA cleared the ACP 215 for the new indications.

Hemorrhage Control Dressing

The Hemorrhage Control (Chitosan) Dressing (CD) is intended to provide a revolutionary improvement in the control of severe life-threatening hemorrhage. The CD is manufactured from Chitosan; a natural biomaterial derived from shrimp shells. It is intended for use by the combat medic/combat lifesaver and other medical personnel on the battlefield.

The FDA cleared the CD for marketing in November 2002. The first CDs shipped in support of OIF went out in March 2003. Since then, approximately 185,000 CDs have been shipped in support of OIF and OEF. To date there have been 60 documented cases of CD use in OEF/OIF. The CD was nearly 100 percent effective and no adverse events were reported.

In September 2005, the CD was transitioned to U.S. Forces Command as executive agent for CD sustainment in the U.S. Central Command area of operations. HemCon, Inc., the manufacturer, achieved full rate production (40,000 units per month) in November 2005.

HemCon, Inc. is seeking to expand the CD's indicated use to include use as an antimicrobial burn dressing. The company is also developing an internal use, fully biodegradable CD variant, for surgical applications.

IV Fluid Warming System

The IV Fluid Warming System is a lightweight, low cost portable fluid warming system, which will deliver 37˚C fluids at flow rates up to 200 ml per minute. The system is compatible with pressure cuffs and pumps, requires low priming volume, and will satisfy 98 percent of all infusion needs.

The manufacturer, Enginivity, Lexington, MA, has fabricated a number of units for evaluation. The results were evaluated at an IPT held with the manufacturer, the Combat Developer and the Materiel Developer. A military need identified was to replace the standard military battery with a rechargeable one. Work to accomplish

this is underway. The FDA approval is expected in FY06.

Rotary Valve Pressure Swing Adsorption Oxygen Generator

The Rotary Valve Pressure Swing Oxygen Adsorption Generator (RVPSOAG) is designed to replace the “D” cylinder for patient care and transport. The RVPSOAG is a substantial simplification of existing pressure swing adsorption oxygen generator technology. The use of a rotary valve, driven directly by a small motor, eliminates complex valve and control systems used in conventional oxygen generators. Taking advantage of the reduced complexity reduces the weight and size of the oxygen generator and increases the efficiency of the generation process. This project will develop a portable device to meet the Combat Developer’s requirements for a portable point-of-use oxygen generator.

The original prototype RVPSOG began commercial production this year. It is being marketed to both the home health care market and military. The manufacturer is continuing the development of a smaller device specifically targeted for use during military evacuations that will be smaller and lighter than a portable oxygen cylinder. This oxygen concentrator will use a new linear compressor. This component is technically challenging because of the required balance of efficiency, durability and cost.

Special Medical Emergency Evacuation Device

The Special Medical Emergency Evacuation Device (SMEED) is a lightweight platform designed to quickly attach to a NATO litter. It was designed by SSG Eric Smeed, while stationed at the U.S. Army Institute of Surgical Research, for medical evacuation of burn patients.

The device is usually mounted over the legs of the patient, although it can be attached anywhere along the length of the litter. The platform has various universal fasteners so that it can be configured in several ways, depending on the mission. It is specifically designed to accommodate all of the Patient Movement Item(s) (PMI) in the Army inventory to include vital signs monitor, infusion pump, aspirator, D-cylinder oxygen tank, ventilator, defibrillator, and has the flexibility to mount other medical devices as required.

More than 700 SMEED systems were deployed with Army, Marine, and Air Force units in support of OIF/OEF. The U.S. Army Aviation and Missile Command (AMCOM) allowed the SMEED to be flown in theater under an emergency restricted Airworthiness Release (AWR). The U.S. Army Aeromedical Research

Lab (USAARL) implemented a new mathematical engineering model to aid AMCOM in its evaluation of the SMEED as candidate for fleet-wide AWR.

Ventilatory Assist Device

The Ventilatory Assist Device (VAD) is an FDA-approved anesthesia delivery system consisting of an anesthesia apparatus, ventilator, and patient ventilator circuit. The VAD will be used to anesthetize patients during surgical procedures with the Field Surgical Teams (FST) and Combat Support Hospitals (CSH). The VAD will eliminate the need for the anesthesia provider to hand bag the patient. Manually ventilating a patient is very labor-intensive and reduces the number of surgical procedures that can be performed. The VAD will be compatible with low-pressure oxygen sources such as oxygen concentrators. The use of the VAD will ensure proper patient ventilation during surgery.

A Milestone C In Progress Review (IPR) was held, to transition the VAD to full-scale production. As a pre-planned product improvement, the manufacturer is integrating the compressor into the ventilator to reduce the weight and size. The compressor will be able to be powered by any electrical power source currently used by military medicine.

Plasma Sterilizer

A plasma sterilizer is being developed which will use ionized hydrogen peroxide vapor to sterilize medical equipment and supplies. This sterilizer will use less power than a conventional steam sterilizer as well as be able to sterilize heat and moisture sensitive items.

The contractor completed the initial design, and is building a prototype sterilizer.

Industrial Services Branch

Introduction

USAMMDA's Industrial Services Branch (ISB), is a small team of engineering technicians with a vast array of design and fabrication skills. This integrated team works together to design, develop drawing packages, and rapidly prototype far forward medical equipment in support of the USAMRMC. The ISB is capable of rapidly prototyping medical devices in a wide range of scales and variety of materials. These capabilities are also used to harden COTS components, equipment and products for use in a field environment.

Military Relevance

In an effort to provide U.S. Forces with innovative, useful and relevant field medical equipment, the ISB collaborates with various organizations within the medical community. This unique USAMRMC resource is instrumental in providing prototype design, fabrication, and evaluation/testing and modifications for products, components and/or systems. Key principals that drive product design are: all products must be functional, simple to operate, small, lightweight, easy to assemble *(no tools),* parts interchangeable and packaged in a low volume cube. The pride we take in innovative design and quality workmanship has produced numerous products and several U.S. patents.

Submersible Bio-monitoring System 2nd Generation

The collaborative efforts involving USAMMDA's ISB and U.S. Army Center for Environmental Health Research (USACEHR) has led to the development of a new and improved 2nd generation submersible bio-monitoring system. Currently, this system, in real-time, monitors and evaluates water quality based on the biological response of eight bluegills. The known behavior parameters of these fish in various water conditions are used as standards to insure water quality. The analysis of electrical signals, emitted from the fish, are first amplified and then fed into a computer software program that records, evaluates and sends an alarm when those signals represent a potential chemical/toxicity problem.

After months of testing the initial prototype unit, user input/recommendations were evaluated and addressed. In an effort to move this product to the next level, design solutions were incorporated to enhance function and ease operation. Providing oxygen was one functional design improvement that was implemented to safeguard the fish during detected periods of low dissolved oxygen. Other improvements were those that made the unit easier to use.

Portable Mini Gas Analyzer

In another collaborative effort, USAMMDA's ISB and the Aberdeen Test Center (ATC) at Aberdeen Proving Ground, leveraged each other's resources to develop/refine a unique mini-gas analyzer. This technology is used to troubleshoot leaks, conduct area sampling and measure occupational exposure levels of toxic gases such as hydrogen fluoride, hydrogen chloride, hydrogen sulfide, hydrogen cyanide and ammonia in the air. Currently, this sampler is utilized to provide key test data to engineers/scientists in their efforts to design and evaluate Military vehicle fire suppression equipment.

Survivability and function are real concerns in a live-fire type testing environment. As a result, the ISB was engaged to provide their expertise in the packaging and hardening of COTS components and to design/fabricate unique items. This effort included electronic circuitry design, programming, fabrication and assembly. Our shared knowledge and resource leveraging enabled this project to advance to a second generation sampler that will have the potential for real time analysis capability.

Model 2 - Rapid Instrumentation Sampling Equipment (M2-RISE)

In a mutual effort between USAMMDA and the Aberdeen Test Center is the M2-RISE, which is a toxic gas sequential "grab" sampler. The culmination of each organization's strengths including, sampling expertise, electronics, and mechanical design/fabrication resulted in this second generation sampler. This sampler was designed, fabricated and assembled, enabling the tester to simultaneously sample up to four different gasses at as many as six different time intervals. As a result of this capability, a greater confidence in realistic test data is achieved, thereby providing system engineers a much desired tool in their efforts to minimize exposure hazards to our military.

PHARMACEUTICAL SYSTEMS

Introduction

The Pharmaceutical Systems Project Management Office (PSPMO) centrally manages the development and acquisition of pharmaceutical and biological products (drugs, vaccines, diagnostics, blood products and resuscitative fluids). These products are fielded as preventive, protective and therapeutic modalities for use against infectious diseases and for combat casualty care. Product Managers leverage domestic and foreign medical technology to remedy deficiencies identified by the Combat Developer and monitor military, industrial, and university research projects for potential solutions to identified problems.

Military Relevance

U.S. Military Forces must be prepared to serve anywhere in the world against any threat. This could result not only in conventional injuries sustained during combat operations, but also from exposure to endemic diseases not commonly found in the United States. The development of products against these threats will help save lives, sustain the Fighting Force and enhance return to duty.

Adenovirus Vaccine, Types 4 and 7

Adenovirus vaccine has been used exclusively by the military to prevent Adenovirus-related acute respiratory disease (ARD) in Soldiers living in barrack-type environments during basic training. The vaccine is an orally administered, enteric-coated tablet containing live adenovirus serotypes 4 or 7. Prior to the use of adenovirus vaccines, adenovirus types 4 and 7 accounted for 60 percent of all ARD in military recruits who were hospitalized. Adenoviruses are associated with pharyngitis, conjunctivitis, atypical pneumonia, and rhinitis. A contract to develop and manufacture the type 4 and 7 adenovirus vaccines was awarded in 2001 to Barr Laboratories, Inc. (Barr's R&D Division is Duramed Research, Inc.). The first phase of the contract required an Investigational New Drug (IND) application and successful completion of Phase 1 clinical trials. The second phase requires completion of all clinical trials and full FDA licensure of the product. Barr completed building construction of the adenovirus manufacturing facility at their Forest, Virginia, laboratory site. All equipment was installed and qualifications performed. During CY 2005, results from the Phase 1 study were analyzed and preparations for extensive Phase 3 testing were begun at Fort Jackson, South Carolina, and Great Lakes Naval Station in Evanston, Illinois. Manufacturing processes were further defined by Duramed. Clinical trials required for licensing of the vaccines are now in planning and are scheduled for initiation late-summer to fall of 2006.

Dengue Tetravalent Vaccine (DTV)

The dengue tetravalent vaccine (DTV) is a live-attenuated virus vaccine for prevention of dengue fever. The DTV contains all four monovalent serotypes grown in fetal Rhesus lung (FRhL) cell culture. The DTV is being developed in collaboration with GlaxoSmithKline Biologicals (GSK). Phase 1 and early Phase 2 studies of the DTV were continued in CY04 to further assess the safety and immunogenicity of DTV in different populations. During CY2005, new lots of the vaccine were produced under Good Manufacturing Practices at the WRAIR bioproduction facility to meet newly imposed FDA regulations. Phase 1 studies of the new vaccine lots were initiated in Thailand through the Armed Forces Research Institute of Medical Sciences (AFRIMS) supported by the WRAIR.

Hepatitis E Virus Vaccine (HEVV)

The HEVV consists of a purified polypeptide produced in insect cells infected with a recombinant baculovirus containing truncated hepatitis E virus (HEV) genomic sequences encoding the viral capsid antigen. The recombinant HEV protein is formulated with an aluminum salt adjuvant. The HEVV is designed to protect DoD personnel and their families from hepatic disease caused by infection with the HEV. This vaccine is also being developed in collaboration with GSK Biologicals. A Phase 2, prospective, randomized, double-blind, placebo-controlled field efficacy trial of the HEVV was completed in Royal Nepal Army personnel in Kathmandu. The two thousand volunteers received either placebo or 20 micrograms of HEV recombinant protein at 0, 1 and 6 months. The study was conducted through AFRIMS with support from the WRAIR. Results from this study demonstrated that this vaccine is highly efficacious. Based on those results, GSK will assume responsibilities for further development of the vaccine, with DoD's continued input as required.

Human Immunodeficiency Virus (HIV) Vaccine

The U.S. Military has focused its HIV vaccine efforts on the development of vaccines which would be protective against viral strains found outside the United States where Forces may be deployed. The HIV vaccine, currently in advanced development, focuses on the strains prevalent in Southeast Asia. The strategy combines two vaccines: a priming inoculation that is designed to stimulate the cellular immune system, and a boosting inoculation that is designed to stimulate the humoral immune system. The former is ALVAC-HIV (vCP1521) (produced by sanofi-aventis), an attenuated canarypox virus which carries HIV genes; the latter vaccine is AIDSVAX® B/E gp120, bivalent synthetic glycoproteins from the

surfaces of the two types of HIV found in Thailand (produced by VaxGen). A Phase 3 trial is currently in progress to determine the efficacy of this vaccine strategy. The study is led by a Principal Investigator and several hundred staff from the Ministry of Public Health of Thailand, along with Mahidol University (Bangkok) and the Royal Thai Army. Sharing sponsorship of this trial with the Army is the National Institute of Health; other collaborators include the WRAIR, AFRIMS, sanofi-aventis, VaxGen, the Jackson Foundation, EMMES and Quintiles.

The clinical trial is designed to determine the ability of the vaccine combination to protect against HIV infection or to modify the rate of disease progression. The trial has enrolled over 16,000 adult subjects, with half receiving vaccine and half receiving placebo in a double-blinded manner. Enrollment has been completed and all immunizations will be completed by mid-Summer 2006. Subjects will be followed for another three years to detect the occurrence of HIV infections. Oversight of the study is provided by a Data and Safety Monitoring Board and a Pharmacovigilance Committee, both with international membership.

Leishmania Skin Test

The disease leishmaniasis occurs in 88 countries around the world and is caused by protozoan parasites transmitted to humans from the bite of an infected sandfly. More than a million new cases of human leishmaniasis are reported annually in the world. Currently, some 12 million people throughout the world suffer from leishmaniasis.

The *Leishmania* Skin Test (LST) is designed to be used to screen U.S. Service members who may have been exposed to *Leishmania* species (parasites) after deployment to *Leishmania*-endemic areas. The skin test for *Leishmania* is made according to the same general principles as the skin test for tuberculosis. The *Leishmania* test is performed by injecting a small amount of purified *Leishmania* proteins under the skin and then measuring any local skin reaction 48-72 hours later. A small bump of 5mm or greater is a positive indication that the individual has been exposed to the *Leishmania* parasite.

As a result of a reevaluation of program priorities, in light of funding available for development efforts, the contract currently in place with Allermed Laboratories, Inc., to produce the LST was placed in a termination phase. However, Allermed received Congressionally-earmarked funding in the FY06 appropriation to continue their work. The PSPMO will continue to monitor the progress of the contract as long as Congressional funding is available.

Topical Antileishmanial Drug, Paromomycin/Gentamicin

Soldiers who contract cutaneous leishmaniasis are currently evacuated to Walter Reed or Brooke Army Medical Centers for treatment. The current standard of care requires 10-20 daily intravenous injections of Pentostam®, an investigational drug based on the metal antimony which is associated with serious side-effects and toxicity that include vomiting, diarrhea, pancreatitis, elevated liver enzymes and, at higher doses, pulmonary edema. As an investigational drug, it is U.S. FDA approved for use only under an IND protocol and must be administered under strict medical surveillance. The Topical Antileishmanial drug Paromomycin (Topical Paromomycin) is a cream made from two aminoglycoside antibiotics, paromomycin (15%) and gentamicin (0.5%) formulated in an aquaphilic base. Topical Paromomycin is being developed to replace Pentostam® as the first-line therapeutic for the treatment of cutaneous leishmaniasis. It provides an effective treatment option to care-givers to sustain soldier and unit performance by: (1) allowing far-forward self-administration of the drug to minimize lost duty days or duty hours with a simplified treatment regimen (versus intravenous dosing Pentostam®); (2) minimizing the administrative burdens to medical personnel; (3) minimizing or eliminating regulatory costs associated with Pentostam®; and (4) helping to mitigate the psychological impacts from the potentially disfiguring disease.

A Phase 2 clinical trial of the current formulation of the topical drug was completed by the Institut Pasteur (in Paris and Tunisia) against Old World Leishmania. Preliminary results indicate that the drug is highly effective (> 90%) against Old World cutaneous leishmaniasis. During CY2005, a contract was awarded to Teva Pharmaceuticals (USA) for scale-up development and manufacture of the drug product for continued clinical testing to support a New Drug Approval Application to the FDA in CY08. Planning for Phase 3 pivotal clinical testing at the Tunisian field site were also begun in CY2005. Also in CY2005, this effort successfully competed for additional funding from the Office of the Secretary of Defense, Defense Acquisition Challenge Program (DACP).

Malaria Rapid Diagnostic Device (MRDD)

The Malaria Rapid Diagnostic Device (MRDD) will be an FDA-approved field deployable, handheld, disposable point-of-care test to rapidly detect the presence of malaria parasites found in the blood samples of patients displaying symptoms of malaria. The MRDD will not require the use of additional equipment to analyze appropriate clinical specimens. The MRDD will facilitate the early diagnosis of malaria infection and prompt medical intervention. Malaria, in its various forms, constitutes a serious infectious disease threat to the U.S. Forces, including operations other than war, in all tropical and sub-tropical regions of the world. The

80,000 malaria cases in Vietnam resulted in a loss of more than a million man-hours. Similarly, in Operation Restore Hope (Somalia) and Operation Uphold Democracy (Haiti), numerous soldiers contracted malaria. Malaria is an acute infection with high morbidity (severe illness) and the potential to rapidly incapacitate large numbers of personnel. Because one type of malaria is often fatal if untreated in non-immune individuals, the diagnosis of malaria must be accomplished for any Servicemember with fever occurring during or after sojourns in a malaria-endemic region. Even though there are MRDDs marketed outside of the United States, U.S. Forces cannot use them until the MRDDs are approved by the FDA for commercial sale in the United States. To that end, for the MRDD, a 510(k) Premarket Notification must be submitted to the FDA. A 510(k) is a scientific regulatory document by which the FDA evaluates the safety and effectiveness of medical devices.

The FDA has determined that the MRDD can be submitted as a de novo 510(k) Premarket Notification versus the previous requirement that the submission be a Premarket Approval Application (PMA). This change is likely to shorten the FDA's internal review time of the submission from one year to three months. A final clinical study, called a True-Negative Clinical Protocol, was conducted in CY2005. Data from this and previous studies are currently being compiled into the 510(k) application which will be submitted by Binax.

Malaria Recombinant Vaccine With Adjuvant Combinations (RTS,S)

The RTS,S malaria vaccine, is being developed in collaboration with GlaxoSmithKline Biologicals, to protect U.S. Forces from falciparum malaria. RTS,S vaccine consists of recombinantly engineered immunogenic fractions of the malaria sporozoite surface coat co-expressed with protective epitopes from the hepatitis B surface antigen. During purification, these proteins self-assemble into particles that form the antigenic component of the vaccine. The vaccine, delivered by intramuscular injection, is formulated in a liquid emulsion containing potent immunostimulants (designated as AS02A) that dramatically enhance the immune response to the RTS,S particles. Lead laboratory is WRAIR. In an effort to enhance the immunogenicity and duration of protection, the RTS,S vaccine is being tested in combination with a new, proprietary adjuvant system (AS01B) and evaluated in a Phase 1/2a safety, immunogenicity and preliminary efficacy trial in U.S. volunteers. The study was completed at the WRAIR Clinical Trials Center in CY2005. Results from this and previous trials indicate that the RTS,S/AS01 vaccine alone will not induce the immunity required for protection of U.S. Forces. Therefore, the strategy has been shifted to examining the use of the RTS,S vaccine in a Prime-Boost combination with an adenovirus vectored malaria vaccine. Studies for the Prime-Boost vaccine will be initiated in late CY2006 and will determine the future direction for this approach.

Combined Camouflage Face Paint (CCFP)

Camouflage face paint now offers more than simple concealment. The new Combined Camouflage Face Paint (CCFP) in stick-type dispensers will be a U.S. Environmental Protection Agency (EPA) registered blend of face paint with DEET insect repellent to provide a minimum of 8 hours of protection against biting insects. Inclusion of insect repellent protection will reduce nuisance factors by repelling insects near the face and help reduce diseases (e.g., malaria and dengue fever) transmitted by biting insects. All CCFP formulations will be used by individual soldiers for protection against biting insects, protection against detection by night vision goggles (the face paint reduces a soldier's near-infrared signature), and for blending into the environment in all military missions.

In CY2005 visual color evaluations of the new stick formulations were performed by the Natick Soldier Center. Additionally, plans were prepared for required non-clinical safety testing of the stick formulations to meet regulations of the EPA. Once the non-clinical testing is completed, an initial clinical efficacy trial will be conducted at the WRAIR under laboratory controlled conditions. Lead lab for efficacy is WRAIR. Lead lab for camouflage is the Natick Soldier Center.

Antmalarial Drug, Tafenoquine (WR238605)

Tafenoquine (WR238605) is an 8-aminoquinoline that has demonstrated antimalarial potential in both pre-clinical and clinical studies. While it has demonstrated potential both as a prophylactic and treatment drug, the original acquisition strategy was focused on development of tafenoquine for prophylaxis of *Plasmodium falciparum* malaria.

Based on the results of an initial field study carried out from late 2000 to early 2001 in Australian soldiers deployed to East Timor comparing tafenoquine to mefloquine, the FDA placed a hold on the tafenoquine IND pending further safety studies. Additional safety data were presented to the FDA in December 2002, after which the FDA allowed the tafenoquine IND to be re-activated effective 19 January 2003. Per FDA direction, a Phase 1 safety trial was subsequently initiated in July 2003 at the Uniformed Services University of the Health Sciences (USUHS) in Bethesda, MD, to closely examine normal volunteer subjects in a double-blind, placebo-controlled prospective fashion for any evidence of effects on renal function or visual function due to administration of tafenoquine. A second study site for this trial was opened in the United Kingdom in late summer 2004. Results of these studies indicate that the drug will be safe for use in U.S. Forces.

In parallel with these safety issues, the USAMRMC industry partner for development of tafenoquine, GlaxoSmithKline, determined that they could not

ethically support Phase 3 prospective clinical trials to investigate the efficacy and safety of tafenoquine for the prophylaxis of malaria in populations where the drug would not be commercially available. This made proving efficacy of tafenoquine for prophylaxis extremely difficult and caused a re-evaluation of the acquisition strategy. A group of DoD malaria experts led by personnel from the WRAIR was convened to address the issue. The result was that the strategy was shifted to focus on development of tafenoquine as a radical cure for treatment of *Plasmodium vivax* malaria which has been rapidly emerging as the DoD's primary malaria threat. A Clinical Development Plan for this approach is in final draft stages.

Tick-Borne Encephalitis Virus Vaccine

Tick-borne Encephalitis (TBE) is a viral infection of the central nervous system transmitted to people by infected ticks. This disease is endemic in several European countries, Russia, and China. Transmission is seasonal and occurs between April and November, particularly in forest and rural areas. The incubation period averages 7-14 days, followed by 1-8 days of fever and flu-like symptoms. Encephalitis occurs in up to 30 percent of infected individuals, requiring many weeks of hospitalization and rehabilitation. Mortality is 1-2 percent in general, but can be as high as 23 percent in the Far East. Once infected, there is no effective curative treatment, only supportive care. However, a TBE virus vaccine has been used in Europe for over 20 years to prevent illness due to TBE virus infection. The vaccine is licensed for use in Europe, but it is not licensed in the United States.

The TBE vaccine effort has remained unfunded due to limited availability of development funds and the relatively low priority of TBE against other infectious disease threats. However, the producer of the TBE vaccine, Baxter Healthcare, has expressed an interest in approaching the FDA concerning licensure of the vaccine in the U.S. The DoD will assist Baxter in this effort.

Hemoglobin-Based Oxygen Carrier (HBOC)

Hemoglobin-based oxygen carriers (HBOC) consist of purified, cell-free hemoglobin (either human or bovine) in physiologic solutions that are intended to provide fluid replacement combined with capacity to carry and deliver oxygen to vital tissues in patients who have suffered serious hemorrhage and require red blood cells but red blood cells are not available. Several candidate products are in various stages of development by small, private manufacturers. At least two products (PolyHeme®, Northfield Laboratories, Inc, Evanston, IL and Hemopure®, Biopure Corp., Cambridge, MA) are in or are ready to begin Phase 3 pivotal testing

for licensure. The PSPMO continues to monitor both of these efforts which are funded in part with Congressionally-earmarked funding.

Hypertonic Saline Dextran (HSD)

Hypertonic Saline Dextran (HSD) is a resuscitation fluid that utilizes 6% high molecular weight dextran and 7.5% sodium chloride. The potential advantage of HSD compared to usual physiologic resuscitation fluids (e.g., 0.9% sodium chloride and Ringer's lactate) is manifold, including reduced logistical load for field medics, improved hemodynamic response in resuscitated patients, and modulation of harmful immune responses after severe shock and resuscitation. HSD is manufactured by a Swedish company (Biophausia AB) and is approved for use in Europe but not in the United States.

In 2004, the Army began collaboration with the National Heart, Lung, and Blood Institute (NHLBI) to compare HSD to traditional resuscitation fluids for treatment of trauma patients in the United States. The NHLBI study was anticipated in late 2005 that if successful will result in FDA approval for marketing in the United States for treatment of trauma. FDA approval is not anticipated before 2008. Again, the PSPMO has continued to monitor this effort.

Red Blood Cells, Extended Life (RBCXL)

Red Blood Cells, Extended Life (RBCXL), is a new additive solution and blood collection system that extends the life of stored, packed red blood cells from 6 weeks to at least 8 weeks. The key to the new process is a new additive solution and a new bag system for collection and storage. Both the additive solution and the bag system have been developed by the University of Cincinnati and the Army during the past 15 years.

During 2004, the Army and the University of Cincinnati worked to settle intellectual property issues and to identify a corporate partner to complete development and bring the new process to market. In 2004, a manufacturer, Hemerus Medical, St. Paul, MN, was licensed exclusively to complete development and marketing. In 2005, a proposal for this effort was submitted to the DoD Technology Transition Initiative (TTI). The proposal was successful and the effort will receive TTI funding in FY06. Development will be continued by Hemerus and the Army, including completion of pre-clinical and clinical development and finalization of a collection system design and production issues.

REGULATORY AFFAIRS DIVISION

Introduction

On 29 September 2004, USAMMDA assumed the mission for Regulatory Affairs (RA) leadership, policy and coordination for the USAMRMC. In support of this new responsibility, an RA Division was created within USAMMDA. The RA organization was originally staffed with the USAMMDA Clinical Trial Branch (CTB), along with representation from the RA Branch of USAMRMC's Deputy for Regulatory Compliance and Quality. The RA staff from USAMRIID was integrated on a detail basis with Dr. Judy Pace-Templeton identified as the overall RA Director for USAMRMC RA (effective in 2005). Due to Dr. Pace-Templeton's retirement, Colonel Jerry Pierson served as acting director from August through December of 2005.

The USAMRMC RA Division is a multidisciplinary team of regulatory affairs and compliance professionals dedicated to support USAMMDA's mission of developing products for the Warfighter. The RA supports the Office of The Surgeon General (OTSG)-sponsored medical materiel development by providing full-service regulatory support to the IPTs; from tech base through advanced development. The RA operations are mandated in 21 USC 321, 331, 343, 346, 348, 350, 351,352, 353, 355, 360, 371, 372, 373, 374, 375, 376, 379, 381, & 42 USC 216, 241, 262, 263. These statutory requirements have been codified as regulatory requirements found in 21 CFR 3, 11, 50, 54, 56, 58, 200 series, 300 series, 600 series, and 800 series. USAMMDA, as the OTSG's (sponsor) representative for the Army regarding medical materiel development, must comply with U.S FDA statutes and regulations.

The RA Division was organized into the following branches:

- Clinical Trial Monitoring Branch (CTMB)
- Regulated Systems Validation Branch (RSVB)
- Regulatory Sponsor and Product Liaison Branch (RSPB)
- Regulatory Communications and Compliance Branch (RACOMM)

Although reorganized, the mission of RA remained unchanged; that being to develop regulatory strategies, policies, guidance documents, and regulatory cost models to facilitate a common understanding and execution of FDA-regulated research throughout USAMRMC. Additionally, the RA Division was expanding in order to be capable of regulatory writing, clinical trial data management, and planning of product testing and accountability. The USAMMDA RA Division is staffed (through assignment and detail) by civilians and contractors (includes clinical monitoring) who are responsible for the maintenance and direction of approximately 55 investigational products, 6 licensed products and 12 master files. During 2005, approximately 331 submissions were prepared and sent to the FDA. This included 5 new IND Applications.

Military Relevance

Military personnel are deployed worldwide and may be exposed to a variety of endemic diseases as well as chemical and biological warfare agents. In many cases, there are no licensed products available for use against these agents and new products must be developed. The RA Division supports the development of new products through coordination of the regulatory strategy to obtain FDA approval for new products and ensuring the regulatory compliance of these products as they advance through the development cycle.

Clinical Trial Monitoring Branch

Introduction

The mission of USAMMDA is to develop new drugs, vaccines and medical devices to protect, project and sustain the lives of Service personnel. To develop quality medical products for U. S. Forces, the Clinical Trial Monitoring (CTM) Branch works to ensure clinical studies are properly conducted as well as to provide recommendations on study design and execution. This section is responsible for providing recommendations on human safety issues, investigating and evaluating adverse reactions encountered during the course of clinical studies, developing and implementing an integrated quality assurance approach to assure safety of volunteers, and acceptability of data for regulatory purposes. The CTM Branch also provides input on study design, data collection methods and data analysis.

The safety and efficacy of many of these products are tested using investigation medical materiel applications with the FDA. As the OTSG's (sponsor) representative for clinical trials, USAMMDA is responsible for ensuring that clinical studies are conducted in compliance with appropriate regulatory requirements. This is accomplished through clinical monitoring performed by the CTM Branch. Monitors participate in site selection, site preparation, training of site personnel regarding the trial, site monitoring and follow-up to ensure compliance. Monitors also participate in evaluation of manufacturing compliance of the test article used in clinical trials. Monitoring visits to the clinical sites, pharmacies and laboratories assure the integrity of clinical data with respect to accuracy, accountability, documentation, and procedures. Integrity is assured through review of case report forms, source documents, medical records, and regulatory documents in comparison to protocol requirements.

Tasks

Monitoring Special Immunization Program (SIP) Protocols at USAMRIID

The SIP Clinic supports the USAMRIID and extramural sites that administer vaccines to provide an added layer of protection beyond standard safety procedures to designated laboratory personnel at risk of exposure to various pathogens and toxins. Studies of vaccines, which remain under IND status, are monitored by CTM. In 2005, 11 INDs, each with active, open protocols having an average of 200 – 300 subjects per protocol, were monitored.

The CTM, in collaboration with USAMRIID Research Serology Laboratory, developed the validation protocols for the PRNT (Plaque Reduction Neutralization Test) and the microagglutination assays, results of which are essential in determining efficacy of various SIP vaccines. The validation protocols were implemented and statistical analyses were performed on retrospective data establishing validation of these assays.

Further, CTM collaborated with the USAMRIID staff and developed training programs for good clinical practice using interactive workshop approaches providing the participants with hands-on applications rather than using a lecture presentation format.

Establish/Monitor Regulatory Files for Force Health Protection Contingency Protocols

The USAMMDA FHP assists the Secretary, DoD, by providing a coordinated program for maintaining the availability of IND products both in times of peace and in war. The CTM Branch monitors these IND protocols for compliance. Along with monitoring, CTM assisted with preparing regulatory files for investigational products which may be used to protect the health of the deployed Force. The CTM Branch also provided oversight and instruction for maintenance of these regulatory files at both domestic and international locations. During the past year, CTM personnel were engaged in protocol development, site initiation, and trial monitoring as well as training for investigators and site staffs with dealing with Force Health Protection and Contingency protocols in Germany and Korea.

Overall

The CTM Branch monitoring expanded to involve utilization of other pharmaceutical monitors and contract monitors due to an increase in workload. Consequently, in addition to monitoring, the CTM Branch performs contract compliance audits for those monitors contracted. Numerous Phase 1, 2 and 3 studies were initiated or continued this year; 17 pre-study site visits; 11 study site

initiations; 99 periodic site visits; 8 verification audits and contract compliance visits; and 7 study termination / close out visits were conducted, for an overall total of 142 monitoring visits in 2005. The USAMMDA's Clinical Trial Monitors traveled over 200,000 miles worldwide to monitor clinical study sites as far away as Nepal, Kenya, West Africa, Tunisia and Thailand, to assist in developing quality medical products for U. S. Forces.

Regulatory Sponsor and Product Liaison Branch (RSPLB)

The RSPLB was created in 2005 as a result of the 2004 Re-engineering task force. The branch has regulatory scientists and medical writers. The role of the regulatory scientist is to act as a liaison to federal regulatory agencies such as the FDA and the Environmental Protection Agency (EPA). The regulatory scientist ensures effective and accurate scientific communication between product managers (PMs) and the regulatory agencies.

The regulatory scientist is the product development and regulatory strategist. Along with other technical members of the IPT, the regulatory scientist develops the regulatory approach or strategy to guide product development and approval or registration by the FDA or EPA. The regulatory scientist reviews all documents in detail to ensure clarity of data presentation, accuracy of data interpretation, logic, consistency and compliance with regulatory requirements prior to endorsement for submission to regulatory agencies. In effect, what the regulatory scientist releases is what gets submitted.

Another role of the regulatory scientist is to provide guidance to the USAMRMC involved in the process of product development, manufacture and assembly of data to ensure that regulatory requirements are met and commitments to regulatory agencies are fulfilled.

The RSPLB also has three highly qualified medical writers. They provide support to principal investigators in writing protocols, annual reports, and investigator's brochures as well as other types of documents that are submitted to regulatory agencies.

In 2005, RSPB supported submissions to 47 open INDs and 44 products in pre-IND development. This branch contributed to over 90 amendments to the various INDs. Regulatory scientists also responded to multiple requests for information from the FDA.

Regulated Systems Validation Branch (RSVB)

The RSVB (newly created in CY2005) provides compliance and technical support to USAMRMC medical materiel development efforts by validating assays, systems, and analytical instruments, and through providing assistance to USAMRMC facilities and laboratories seeking to attain compliance with USAMRMC standards and/or federal regulations. In CY 2005, RSVB supported both tech base and advanced development projects, including:

- Validation of the Automated Bioaerosol Exposure System (ABES), developed by the Division of Aerobiology, USAMRIID.
- Validation of several analytical instrument in the Department of Virology and the Department of Immunology, AFRIMS
- Development of system-related SOPs for AFRIMS
- Assay Validation support in the Department of Immunology, AFRIMS
- Systems validation consultation and validation documentation review for the USAMRMC Laboratory Information Management System (LIMS)
- Development of SOPs to qualify regulated systems and computer workstations within USAMRIID.
- Development of Equipment Qualification Protocols (EQPs) for USAMRIID
- Development of SOPs and EQPs to establish a quality system within the Biothreat Characterization Center (BTCC)
- Development of budgeting and project management systems/databases to support USAMRMC Regulatory Affairs
- Development of USAMRMC Policies and Pamphlets
- Data Management and validation support to the Special Immunizations Program (SIP), USAMRIID

Regulatory Communications and Compliance Branch (RACOMM)

At the beginning of 2005, RACOMM was staffed with one each Chief/RA Scientist, contract RA Scientist, contract administrative individual and a contract Regulatory Product Development Support individual. During the reporting period, RACOMM gained two RA Specialists (one new hire, and promoted the Regulatory Product Development Support individual), one archivist/database/information manager, one Document Control Manager and a Regulatory Compliance Trainer. In March, the contract RA scientist was transferred to another branch within the Division.

Accomplishments

In an attempt to better organize workload and ensure that sponsor responsibilities were being met, the various activities/sponsor responsibilities were organized into colored zones or functional areas. Activity/accomplishment in the zones is as follows:

Orange Zone (Safety): During the reporting period, staff developed the process by which serious adverse event reports would be received, tracked and routed between the various organizations for review and action. Once finalized, the process was captured in a Visio diagram. In addition, templates were created to support these internal processes as well as for faxing SAE information to the FDA. Staff and representatives from the Medical Research Information Technology System (MeRITS) and Medical Affairs initiated activity to standardize safety reporting language for inclusion into research protocols and develop standard case report forms and a database.

Yellow Zone (Document Control): Staff established a system for providing regulatory update information concerning each IND, master file or NDA to investigators, product managers and commanders. Distribution lists for email were created for each IND/protocol as well as a template created for the creation of each distribution list. The current scanning sheet was revised to reflect the individuals requiring notification or copies of documentation. In addition, activity was initiated to develop a document control database and to reset existing FDA correspondence files in chronological order.

Blue Zone (Submission Mail out): RACOMM initiated the use of green return receipt cards so that the date of receipt of submissions to the FDA could be obtained. Green cards were later replaced by “Coral” sheets as these were more cost effective and had a faster turn around time. This information was tracked on a “submission tracking” log that is posted for viewing by USAMMDA, CBMS and other organizations. To increase consistency, standard templates were created for various submission types to the FDA. Contact information on FDA correspondence was changed to provide a central point of entry for incoming telephone, email and facsimile communications. RACOMM met with representatives from the Department of the Army Printing Service (DAPS) to arrange for large submissions to be printed by this organization. DAPS has been used several times over the past year for both regulatory submissions and training event materiel.

Green Zone (Submission Preparation): The current “Submission Tracking” Log was revised to better track location of regulatory submission through the internal review/staffing process as well as to identify regulatory requests requiring action. The OF 41 originally used to staff submissions was replaced by a color-coded “Routing and Transmittal Sheet” designed to better capture required information/dates. Checklists for various submission types were created to assist with the preparation and review of regulatory submissions.

Purple Zone (Livelink/Information Management): Activity to create the Regulatory Affairs Baseline Information Database (RABID) was initiated during this reporting period. The RABID contains both regulatory and product management information and was created for use by the regulatory scientists and product managers (Advanced Development and MIDRP) to track the status of the various INDs and

associated protocols. A webpage containing tools for the RA Scientists as well as a variety of other useful information was created and posted on the USAMMDA drive.

Dark Blue Zone (Training): Staff initiated activity to standardize position responsibilities so training requirements for each position could be established, and also created a process for routing training requests for appropriate review and approval. Approximately 22 training events were hosted by the RACOMM staff and included support to individuals from MeRITS in creating various training programs including initiation on the Regulatory Affairs Training Program Pamphlet.

The monthly sponsor's responsibilities and oversight committee meetings and support to regular pharmacovigilance meetings in order to work through issues identified in the conduct of the Phase HIV vaccine trial, were also facilitated.

In August 2005, RACOMM communication processes and procedures were reviewed as part of the Command Staff Assistance Visit. The visit revealed no areas requiring action or improvement.

MEDICAL AFFAIRS / FORCE HEALTH PROTECTION

Introduction

USAMMDA assumed the role as the executive agent for the management of the DoD's Force Health Protection (FHP) program. In February 2004, USAMMDA established an FHP to plan, implement, and sustain DoD directed FHP IND protocols and to train the investigational staff in the execution of these protocols according to FDA regulatory guidelines. The FHP office currently has four product managers overseeing 10 IND protocols and they coordinate the myriad of administrative, clinical and regulatory activities needed to successfully activate and sustain these protocols worldwide.

Military Relevance

Military personnel deployed in particular military operations could potentially be exposed to a range of chemical, biological, and radiological weapons as well as diseases endemic to an area of operations. FHP is an organized program of healthcare preventive or therapeutic treatment, or preparations for such treatment, designed to meet the actual, anticipated, or potential needs of a group of military personnel in relation to military missions. It is DoD policy that personnel carrying out military operations shall be provided the best possible force health protection, including safe and effective medical countermeasures to chemical, biological or radiological warfare and endemic disease threats. The FHP office manages those medical countermeasures. Current medical countermeasures include FHP products for the prophylaxis or treatment of Smallpox and the complications from severe reactions to smallpox vaccine, anthrax, botulism, Crimean-Congo hemorrhagic fever, Lassa fever, Leishmaniasis, and Korean hemorrhagic fever. The FHP IND protocols are listed in the table below:

IND No	Title
65480	Department of Defense Protocol for the Use of Cidofovir (VISTIDE®) as a Treatment for Adverse Reactions Associated with Vaccinia Virus Vaccination
65480	Department of Defense Contingency Protocol for Emergency Use of Cidofovir (VISTIDE®) as a Treatment for Smallpox
10999	Protocol for the Intravenous Administration of Vaccinia Immune Globulin (Human) Liquid Formulation to Treat Complications from Vaccination with or Accidental Exposure to Vaccinia Virus
BB-IND 3723	Protocol for Vaccination of Selected Volunteers with Pentavalent Botulinum Toxoid to Protect against Botulinum A Toxin Toxicity
BB-10,621	Emergency Use of Investigational Heptavalent Equine-Based Botulinum Antitoxin (Types A, B, C, D, E, F, and G) After Exposure to Clostridium botulinum or Other Closely Related Bacterial Species
BB-IND 10081	Contingency Protocol for Anthrax Vaccination to Protect against Bacillus anthracis Spores

Accomplishments – 2005

Emergency Use Authorization

Bioshield provisions of the 2004 National Defense Authorization Act identified procedures for the use of an Emergency Use Authorization (EUA) that allows DoD to request use of a non-FDA approved product (investigational product) in the event of a national emergency. The FHP office under the BioShield provision collaborated with the Centers for Disease Control (CDC) in the submission to the FDA, the necessary documents to allow for the activation of an EUA for "Request For Emergency Use Authorization for The Use Of The Anthrax Vaccine Adsorbed (AVA, BioThrax ^{TM}) To Protect Individuals After Potential or Confirmed Exposure to Anthrax Spores". The FHP is also collaborating with the CDC in the submission of the FDA documents to allow activation of an EUA for the following disease states:

Plague	Use of Gentamicin for Treatment of *Yersinia pestis* (Plague) in the Event of a Bioterrorism Event
Plague	Use of Ciprofloxacin for Pre and Post Exposure Prophylaxis and Treatment of Plague in the event of a Bioterrorism Release of *Yersinia pestis*
Tularemia	Use of Gentamicin for the Treatment of Tularemia in the Event of a Bioterrorism Release of *Francisella tualrensis*
Tularemia	Use of Ciprofloxacin for the Treatment and Pre and Post Exposure Prophylaxis of Tularemia in the Event of a Bioterrorism Release of *Francisella tualrensis*
Botulism	Use of H-BAT (Intracel) After Exposure to *Clostrium botulinum* or Other Closely Related Bacterial Species Due a Bioterrorism Incident or a Naturally Occurring Outbreak

Force Health Protection Related Accomplishments

In April 2005, the FHP office was tasked to stand up two Special Medical Augmentation Response-Investigational New Drug (SMART-IND) Teams to provide training, guidance, and facilitate the availability of investigational drugs, vaccines, and medical products during disaster, civil-military cooperative action, humanitarian, and emergency response to Chemical Biological Radiological Nuclear Explosive (CBRNE) or infectious disease incidents in the Continental United States (CONUS), United States territories or possessions, and Outside Continental United States (OCONUS) unified command areas of responsibility.

The SMART-IND Teams are designed to deploy on request of legitimate civil, Federal, or defense authorities, using appropriate, recognized and approved channels, either regionally or to other national incident sites to provide short duration medical augmentation to regional domestic, Federal, and Defense

agencies responding to a disaster, civil military cooperative action, humanitarian, and emergency incidents. The SMART members' principal role is to support, provide technical advice, assess, train on use of investigational products and FDA Good Clinical Practice regulatory requirements, and provide liaison to units or activities in the designated mission area of responsibility (AOR).

During the calendar year 2005, the FHP office was actively involved in the writing of FHP IND protocols, establishing new sites, activating, and sustaining these protocols in accordance with strict regulatory guidelines worldwide.

OCONUS: As part of their regulatory activities, the FHP office provided continuous regulatory support for all of the FHP-IND protocols including continuing review and required periodic reports to the FDA, receipt and processing of FHP IND products and data from sites where these products are located. Being acutely aware of the logistical trail associated with any investigational product, the FHP office is collaborating with the USAMMA to establish a Memorandum of Agreement to coordinate medical logistics activities in support of FHP contingency protocols in their respective AOR.

Educational Training and Regulatory Affairs Activities

As part of their overall educational and training strategy, the FHP office planned and deployed a team of 6 members to provide a 4-day, FHP training course to the 121st General Hospital, Yongsan, South Korea, and Landstuhl Regional Medical Center organic assets, Landstuhl, Germany, to enhance their ability to administer FHP-IND products in compliance with FDA regulatory guidance.

The FHP office leverages technologies by collaborating with EduNeering in the creation of a new "web-based" Good Clinical Practice (GCP) training course to assist FHP IND protocol principal investigators and clinical associates fulfill their FDA regulated GCP training requirements. This effort had a two-fold impact: 1) providing the required training to FHP personnel in a timely and efficient manner and; 2) it will save the MEDCOM thousands of dollars in TDY costs usually incurred when personnel have to travel (OCONUS and CONUS) to attend civilian GCP training programs.

Finally, the FHP office provided proactive leadership by coordinating and directing the quarterly meetings for the DoD's Force Health Protection IND Steering Committee.

***** Investigational New Drug (IND): Any drug or vaccine (collectively termed "drug") which is unapproved (by FDA) for its current indication. Classically, a drug is in IND status while it is under development (pre-FDA approval) but must be used in humans to demonstrate its safety and efficacy to the FDA. A drug may remain in IND status if its safety profile makes it acceptable for use in humans but the disease (e.g., botulism) precludes conducting efficacy studies to show that it

works in humans (unethical to expose humans to live botulism). When a drug is in IND status, even if used for Force Health Protection, it must be administered under an approved protocol, just like it was being used in a clinical study, and extensive documentation of all aspects of “the study” must be kept, including custody of the drug, qualification of participants, informed consent, administration of the drug, adverse reactions, scheduled follow-up of participants, disposition of the subject, disposition of the drug. This is difficult and labor intensive under normal circumstances in controlled conditions (i.e., research clinical study). On the battlefield, the challenges are magnified astronomically.